

Title: Interleukin-1 Blockade in HF with Preserved EF (D-HART2)

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Interleukin-1 Blockade in Heart Failure with Preserved Ejection Fraction (HFpEF)

A Randomized Placebo-controlled Double-blinded Study

D-HART2 study

STUDY PROTOCOL

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Virginia Commonwealth University

Prior versions and edits:

Edits to Version 1: 08132014

- **Blood pressure measurement through ccNexfin finger cuff, section 7.8 and 7.13:** The ccNexfin “finger cuff” has been added for continuous blood pressure monitoring throughout the exercise protocol. Patients will also undergo brief blood pressure cuff inflation/deflation to measure flow-mediated dilatation prior to exercise.
- **Bioelectrical Impedance (Bio-Impedance) to measure body composition, section 7.9 and 7.13:** Four electrodes will be applied to the skin, a small amount of electricity will be ran through the body to measure bioelectrical impedance (bio-impedance) to determine body composition.

Edits to Version 2: 09072014

- **Personnel:** The list has been updated.
- Sections 5.2 and 7.12 – The description of the biomarkers has been clarified in more detail.
- Section 7.1 – It is now explained that the patient will receive the investigational drug in 2 batches, one for 5 weeks and a second one for 7 weeks.
- Section 7.6 – The timing of follow up visits has been clarified in more detail.
- Section 8.3.1 – The definition of “related” and “unrelated” to research has been clarified in more detail.

Edits to Version 3 04062015:

- Personnel have been updated.
- The University of Virginia has been removed from the list of potential alternate sites as site initiation will no longer be an option.
- Health Diagnostic Laboratories is now known as True Health Diagnostic Laboratories and this change has been updated.
- The procedures for the whole blood assay have been removed as this analysis is not being conducted during the study.
- “Any abnormal laboratory test” will no longer be considered an adverse event.
- The definition of Adverse Events (AEs) has been revised, and reporting plan clarified.

Edits to Version 4 11282015:

- Screening will be performed in the whole VCU Health System, not just in the VCU Pauley Heart Center, as previously described (Section 6.1).
- Requirement for “prior hospitalization for heart failure” has been removed from inclusion criteria (Section 6.2, and Appendix B forms).

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Appendix: DSMB Chapter for D-HART2

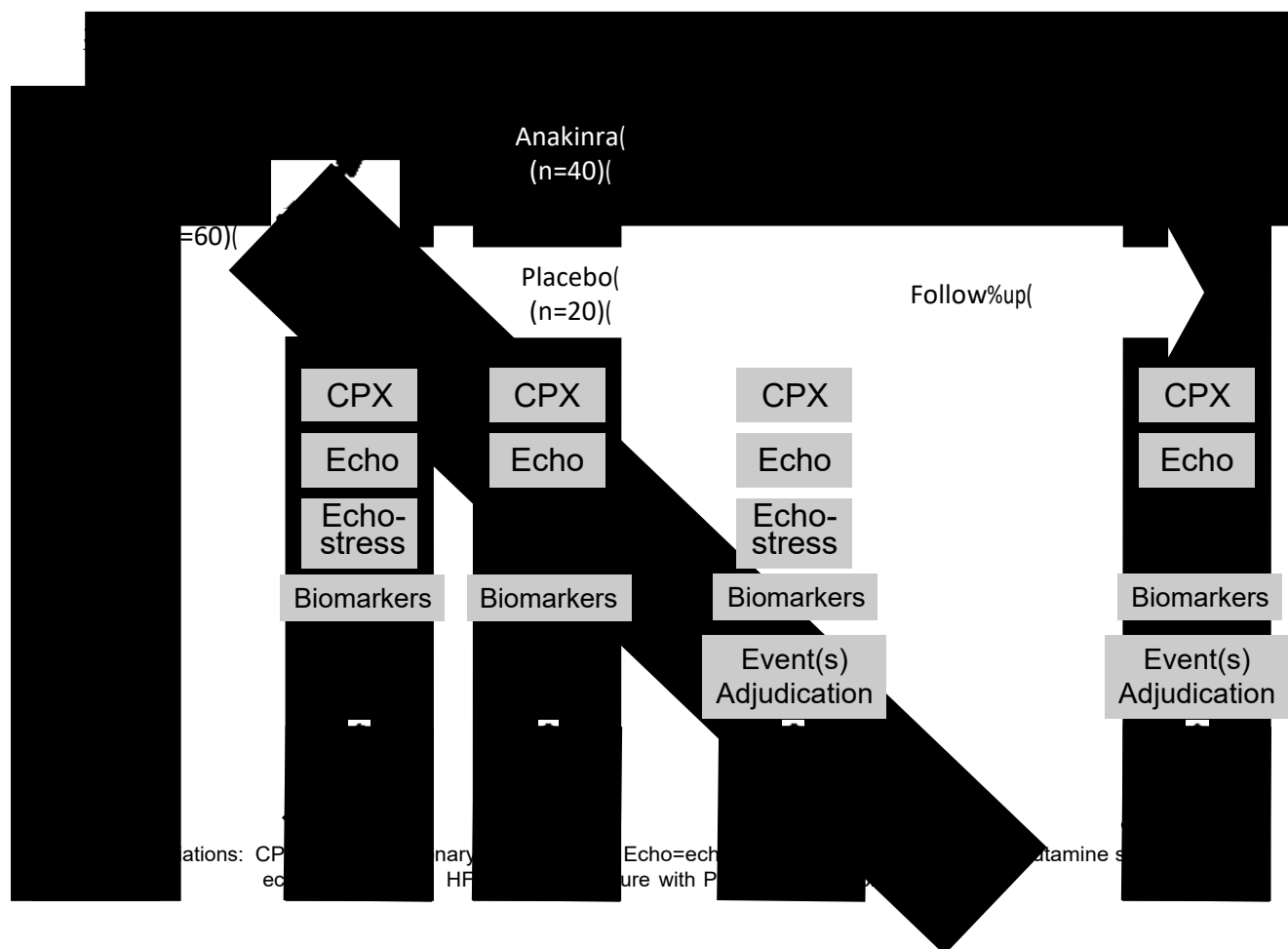
1) PERSONNEL

Name	Role	Institution/ Division
Antonio Abbate, MD/PhD	Co-Principal Investigator	VCU, Cardiology
Benjamin Van Tassel, PharmD	Co-Principal Investigator	VCU, School of Pharmacy
Ross Arena, PhD	Investigator	University of Illinois, Chicago, IL
Justin Canada, EPC	Exercise Physiologist	VCU, Physical Therapy
Salvatore Carbone, MS	Research Assistant	VCU, Cardiology
Robin Sculthorpe, PharmD	Investigational Pharmacy	VCU, School of Pharmacy
Michael C. Kontos, MD	Event Adjudicating Committee	VCU, Cardiology
Keyur Shah, MD	Event Adjudicating Committee	VCU, Cardiology
Elizabeth Miller, MD	Event Adjudicating Committee	VCU, General Medicine
Dominick Angiolillo, MD	DSMB Chair	University of Florida, Cardiology
Richard Cooke, MD	DSMB member	VCU, Heart Failure
Gonzalo Bearman, MD	DMSB member	VCU, Infectious disease
Ion Jovin, MD	DSMB member	VCU, Cardiology / McGuire VA
Jeffrey Kushinka, MD	DSMB member	VCU, General Internal Medicine
Christine DeWilde, RN	DSMB coordinator	VCU, Pulmonary
Juan Lu, PhD	Consultant	VCU, Biostatistics
Kenneth Ellenbogen, MD	Consultant	VCU, Cardiology
John (Ian) Nixon, MD	Consultant	VCU, Cardiology
Charles A. Dinarello, MD	Consultant	University of Colorado
Pierluigi Tricoci, MD	Consultant	Duke University
Filippo Crea, MD	Consultant	Catholic University, Rome, Italy
Giuseppe Biondi-Zoccai, MD	Consultant	Sapienza University, Rome, Italy

Abbreviations: DSMB=Data Safety Monitoring Board

2) PROTOCOL SUMMARY

Title:	Interleukin-1 Blockade in Heart Failure with Preserved Ejection Fraction (HFpEF)
Population:	60 patients with a clinical diagnosis of heart failure, a recent imaging study documenting LV ejection fraction >50% and evidence of diastolic dysfunction, and CRP >2 mg/L
Site(s):	Virginia Commonwealth University, Richmond, VA
Study Duration:	24 months
Description:	Phase II clinical trial of Anakinra for the treatment of heart failure with preserved ejection fraction, impaired left ventricular relaxation, and increased systemic inflammation (CRP>2 mg/L)
Objectives:	To determine the effects of IL-1 blockade with Anakinra on peak of aerobic exercise capacity (peak VO_2) and ventilatory efficiency ($\text{V}_E/\text{V}_{\text{CO}_2}$) measured with a cardiopulmonary test in patients with heart failure with preserved ejection fraction
Study Design:	Single-center, randomized, double-blinded, placebo-controlled clinical trial with allocation to Anakinra 100 mg daily or placebo in 2:1 ratio for 12 weeks
Estimated Time to Complete Enrollment:	15 months



4) BACKGROUND INFORMATION AND SIGNIFICANCE

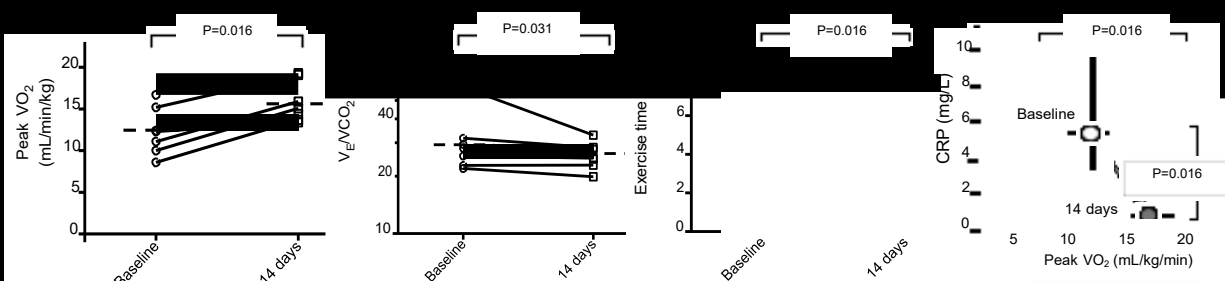
Heart failure (HF) is a condition in which the heart can no longer pump enough blood to the rest of the body or it is unable to do so without significantly increasing the filling pressure. HF is characterized by dyspnea, fatigue, and declining cardiac function. Poor exercise capacity is a common finding among HF patients and imposes a significant detriment to quality of life. Quantifiable measures of exercise capacity such as peak oxygen consumption (peak VO_2) and the minute ventilation and carbon dioxide production slope (VE/VCO_2) represent strong independent predictors of HF mortality and hospitalization.

Despite the clear improvements in the treatment of cardiovascular disease over the past several decades, the incidence and prevalence of HF have not decreased, survival has marginally improved, and morbidity remains unacceptably high.^[1-3] There is an urgent need to develop novel therapeutic approaches to alleviate symptoms, improve functional capacity and quality of life, slow disease progression, and reduce hospitalization.

Interleukin-1 (IL-1) is a key pro-inflammatory mediator in innate immunity that induces synthesis and expression of multiple secondary inflammatory mediators (i.e. Interleukin-6 [IL-6],

Interleukin-18 [IL-18], C reactive protein [CRP]).^[4] Early descriptions also noted that very small concentrations of IL-1 could induce a sepsis-like syndrome associated with cardiac dysfunction and described the fine regulation of the synthesis and release of this cytokine.^[5] Two related genes code for two different proteins IL-1 α and IL-1 β , both binding the same IL-1 receptor (type I). IL-1 β is the main form of circulating IL-1, binding to the membrane IL-1 receptor in the same cell (autocrine), neighboring cells (paracrine), or entering the circulation targeting distant cells (endocrine). IL-1 α , on the other hand, is mostly expressed as a membrane-bound protein or released from the cytoplasm during cell death. An additional gene codes for IL-1 receptor antagonist (IL-1Ra), a protein that binds to the IL-1 receptor but does not exert agonist activity, and functions as a naturally occurring anti-inflammatory protein.^[4]

Exogenous also IL-1 β induces a reversible and dose-dependent contractile dysfunction *in vitro* or *in vivo* in the mouse.^[4,6] These observations formed the basis for an open-label, single-arm, proof-of-concept study to test the safety and feasibility of IL-1 blockade in patients with stable HFrEF and elevated CRP (>2 mg/L), and determine the effects on aerobic exercise capacity (ClinicalTrials.gov NCT01300650).^[7] We enrolled patients (n=8) with stable chronic HFrEF as evidenced by no recent hospitalizations (within previous 12 months), no recent medication changes (within 3 months), and screening CRP >2 mg/L. Patients received 14 days treatment with daily anakinra 100 mg subcutaneous injection starting after the baseline cardiopulmonary exercise testing (CPX) to evaluate the co-primary endpoints of peak VO₂ and VE/VCO₂ slope at the beginning and end of the study. Of the 8 patients enrolled, 1 experienced flu-like symptoms during the study and withdrew after 8 days of injections (symptoms resolved spontaneously with 3 days of discontinuation). All 7 patients who completed the protocol experienced improvement in peak VO₂ after 14 days anakinra treatment; 6 out of 7 patients experienced improvement in the VE/VCO₂ slope after 14 days anakinra treatment (Figure 2). Patients also experienced significant improvements in secondary endpoints of total exercise time and oxygen utilization efficiency score. To verify the achievement of IL-1 blockade, we found a 80-90% reduction in median plasma of CRP, IL-6, and IL-1 β , without measurable changes in TNF α . While there was no significant association between peak VO₂ and CRP, there appeared to be trend toward improved peak VO₂ with lower CRP (Figure 2). No significant changes occurred in resting heart rate (HR), maximum HR, resting blood pressure, maximum blood pressure, or heart rate



2. Treatment with anakinra for 14 days led to an improvement in aerobic exercise capacity and a reduction in CRP in an open-label proof of concept study in patients with HFrEF. Modified from Van Tassel et al. *PLOS ONE* 2012.

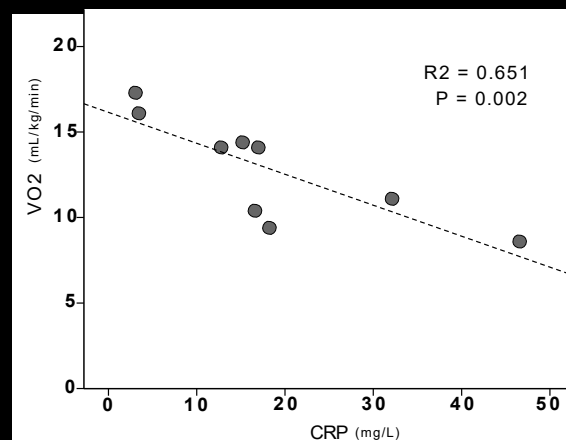
The role of IL-1 in HFpEF or diastolic dysfunction is less established. IL-1 induces cellular hypertrophy and changes in calcium handling *in vitro*. Mechanisms involved in the pathogenesis of HFpEF.^[8] Similar effects

are induced by other inflammatory mediators downstream of IL-1 β .^[9] We have recently found that in the mouse *in vivo* IL-1 β induces reversible and dose-dependent alterations in diastolic function (Figure 3). Moreover, IL-1 β also blunts the contractile response to β -adrenergic stimuli (isoproterenol), an additional mechanism potentially involved in exercise intolerance in HFpEF.

From a clinical standpoint, patients with chronic IL-1-mediated diseases such as patients with rheumatoid arthritis are more likely to have left ventricular hypertrophy and diastolic dysfunction.^[10,11] In a study of 23 patients with rheumatoid arthritis, a single dose of anakinra 100 mg improved left ventricular diastolic function as well as coronary flow reserve and flow-mediated brachial artery vasodilatation,^[12] suggesting that IL-1 blockade may represent a viable treatment strategy. More recently, studies in patients with critical illness, a condition characterized by intense inflammation, more than diastolic dysfunction,^[13] and the presence of diastolic dysfunction and elevated inflammatory biomarkers.^[9]

In our own pilot feasibility study of patients with HFpEF, elevated CRP levels (a marker of inflammation) correlated with reduced exercise capacity (peak VO₂) (Figure 4).

In the current proposal, we propose that IL-1 contributes to the exercise intolerance observed in HFpEF. We hypothesize that IL-1 characterizes patients with HFpEF by modulating cardiac relaxation, contractile reserve, and other endothelial function, and we propose to investigate IL-1 blockade with anakinra as a potential therapeutic strategy to improve quality of life and reduce morbidity in HFpEF.



Preliminary data show a significant inverse between CRP levels and peak VO₂.

5) OBJECTIVES

The current research is designed to investigate the safety and efficacy of Anakinra in heart failure patients with preserved ejection fraction, evidence of impaired left ventricular relaxation, and elevated CRP levels (as a marker of inflammation) in a randomized double-blinded trial. We hypothesize that blockade of IL-1 will improve exercise capacity in these patients.

5.1 Primary Endpoint(s)

Absolute changes in aerobic exercise capacity (peak VO_2) and ventilatory efficiency (VE/VCO_2 slope) after 12 weeks treatment will be considered co-primary endpoints. This will compare patients treated with anakinra (N=40) vs placebo (N=20), and provide a randomized, double-blinded assessment of the effects of IL-1 blockade on aerobic exercise performance. The data will be collected and electronically transferred to the core laboratory at the University of Illinois, Chicago, IL.

5.2 Secondary Exploratory Endpoints

Additional endpoints will include parameters measured at CPET, echocardiography, as well as biomarkers, and clinical outcomes.

Cardiopulmonary Exercise Test (CPX) parameters: in addition to the changes from baseline in VO_2 and VE/VCO_2 at 12 weeks (which constitute the co-primary endpoints), secondary endpoints will compare changes in VO_2 and VE/VCO_2 at 4 and 24 weeks in patients treated with anakinra versus placebo. This will help determine when the peak effect of IL-1 blockade is achieved, the duration of effects after cessation of therapy, and the presence of any rebound effects. We will also analyze changes in heart rate and blood pressure during exercise and during recovery to assess chronotropic competency and heart rate recovery. The data will be collected and electronically transferred to the core laboratory at the University of Illinois, Chicago, IL.

Echocardiography: structural and functional echocardiographic parameters include left and right ventricular dimensions, mass, systolic and diastolic function. These will provide mechanistic insight as to whether the hypothesized changes in aerobic exercise performance are dependent upon changes in cardiac dimension/function. The data will be collected and electronically stored for further analysis at the conclusion of the study.

Exercise stress echocardiography: Exercise stress echocardiography will be performed at baseline and 12 weeks to measure diastolic and contractile reserve. We will perform an assessment before initiation of exercise and immediately after cessation of peak exercise.

Questionnaires: Two independent questionnaires will be used to assess quality of life and HF symptoms. The Minnesota Living with Heart Failure questionnaire (MLHFQ) is a 21-question graded questionnaire that has been extensively used to measure impairment in quality of life in patients with HF.^[14] The Duke Activity Status Index (DASI) questionnaire is a 12-question, yes/no, instrument that allows for the calculation of perceived functional capacity,^[15] in which each question describes a different physical activity and the questions are weighted according to their degree of physical exertion. Both questionnaires will be administered at 0, 4, 12 and 24 weeks in accordance with CPET and echocardiography. The data will be collected and electronically stored for further analysis at the conclusion of the study.

Biomarkers: Blood will be collected at each timepoint throughout the study (0, 4, 12, and 24 weeks) and analyzed for complete blood cell count, metabolic markers (including lipids and lipoproteins, glycemic control and insulin resistance, liver and renal panel, sterols), inflammatory

markers (i.e. high sensitivity CRP) and cardiac biomarkers (i.e. NT-proBNP and troponin I). The data will be collected and electronically stored for further analysis at the conclusion of the study.

Clinical outcomes: Incidence of death (cardiac and non-cardiac), hospitalizations (for HF, for other cardiac causes not related to HF, or for non-cardiac reasons) will be recorded at 4, 12, and 24 weeks in every patient, and then every 12 weeks until study conclusion (max 108 weeks). The investigators and clinicians caring for the patients will remain blinded to treatment allocation and to the CRP data. Adjudication of events will be performed by an *ad hoc* committee blinded to treatment allocation and to CRP data.

6) ENROLLMENT IN THE STUDY

6.1 Screening

Patients will be screened by the investigators in the VCU Pauley Heart Center Inpatient and Outpatient services during the course of their regular clinical care. A waiver to obtain authorization by the subjects to access personal health information during screening process has been obtained from the IRB. Those who meet entry criteria will be approached by the investigators for enrollment. Potential subjects will be provided with an Informed Consent Form in accordance with the local Institutional Review Board. Enrolled subjects will then undergo complete screening for entry criteria (listed below). Where possible, investigators will rely on clinically available laboratory results; the remaining laboratory analyses will be ordered and billed to the study account. The central laboratory at VCU Hospitals will be used for all clinically available tests. Point-of-care testing may be used for the determination of the plasma CRP levels. Should enrollment fall behind this goal, we will pursue recruitment at other community-based centers in Central or Northern Virginia.

6.2 Subject Inclusion and Exclusion Criteria

In order to be eligible for this study, patients must meet ALL the 4 Inclusion criteria and NONE of the Exclusion criteria.

INCLUSION CRITERIA:

- 1) Symptoms and signs of heart failure (NYHA II-III)
- 2) Recent Imaging Study (<12 months) showing LVEF>50% and LVEDVI<97ml/m²
- 3) Evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness as shown by one of the following
 - a. Invasive Hemodynamic measurements
 - i. mPCW >12
 - ii. LVEDP>16mmHg
 - b. Tissue Doppler Echocardiogram
 - i. $E/E' >15$

ii. *E/E' 8-15* and one of the following

- LVH
- Afib
- LAE
- $E/A < 0.5 + DT > 280$

c. Biomarkers

- i. $BNP > 200 \text{ pg/ml}$ (not due to a concomitant disease such as pulmonary arterial hypertension, pulmonary embolism, acute renal failure, or other)

4) $hsCRP > 2.0 \text{ mg/L}$

EXCLUSION CRITERIA:

- Age < 21
- Concomitant conditions or treatments which would affect completion of the study or interpretation of the study tests including but not limited to the following conditions:
 - physical inability to walk or run on a treadmill
 - angina or evidence of spontaneous or inducible ischemia
 - uncontrolled arterial hypertension
 - atrial fibrillation (or other arrhythmias)
 - moderate to severe valvular heart disease
 - chronic pulmonary disease
 - anemia ($Hgb < 10 \text{ g/dl}$)
- Angina, uncontrolled hypertension or electrocardiograph (ECG) changes (i.e. ischemia, arrhythmias) that limit maximum exertion during cardiopulmonary exercise testing
- Anticipated need for surgery
- Active infection including chronic infection
- Active cancer (or prior diagnosis of cancer within the past 10 years)
- Recent (< 14 days) or active use of immunosuppressive drugs (including but not limited to high-dose corticosteroids [$> 1 \text{ mg/kg}$ of prednisone equivalent], $TNF-\alpha$ blockers, cyclosporine) not including NSAIDs or corticosteroids used for IV dye allergy only)
- Chronic auto-immune or auto-inflammatory disease (including but not limited to rheumatoid arthritis, systemic lupus erythematosus)
- Neutropenia (absolute neutrophil count $< 1,800/\text{mm}^3$ [or $< 1,000/\text{mm}^3$ in African-American patients])
- Severe impairment in renal function (estimated glomerular filtration rate $< 30 \text{ ml/kg*min}$)
- Recent or planned use of vaccination with live attenuated viruses
- Allergy to rubber or latex
- Allergy to products derived from *Escherichia coli*
- Pregnancy or breastfeeding
- Inability to give informed consent

7) STUDY DESIGN

We designed a single center, placebo-controlled, double-blinded randomized study of Anakinra in patients with heart failure with preserved ejection fraction (HFpEF). Patients will undergo baseline clinical assessment, CPET, echocardiogram, exercise stress echocardiography, and blood tests for biomarkers. The CPET, the echocardiogram and blood tests will be repeated at

each visit (4, 12 and 24 weeks). The exercise stress echocardiogram will be repeated after 12 weeks of treatment. See Schematic of Study Design (3).

7.1 Treatment with Anakinra

Anakinra and matching placebo syringes will be provided by the manufacturer, Swedish Orphan Biovitrum (SOBI, Stockholm, Sweden) to the Investigational Pharmacy at the coordinating center at VCU, where the syringes are stored until ready to be administered to the patient. SOBI has also guaranteed a continuous supply of anakinra and placebo should the current supply expire prior to completion of the trial.

After completion of all baseline testing patients will be given a 5-week supply of Anakinra or placebo, and will be instructed on how to store and self-administer the drug once daily (approximately at the same time every day). We added an extra 7-day supply in case of a need to delay Visit 2 of few days. An additional 7-week supply of Anakinra or placebo will be given on Visit 2 (4 weeks). The patient will also be educated on expected side effects and need to inform the investigators about any foreseen and unforeseen events. A sharp container sufficient to contain all 60 syringes will be given to the patient to dispose the syringes in, and to bring back at the each visit.

7.2 Allocation concealment

Anakinra or placebo (vehicle) will be supplied by the manufacturer of Anakinra (Kineret™, Swedish Orphan Biovitrum, Stockholm, Sweden), dispensed in small syringes (1 ml), provided to the patient for daily subcutaneous injection. The syringes for Anakinra or placebo will be undistinguishable. The randomization log will be prepared by a consultant outside the institutions involved in the enrollment (Giuseppe Biondi-Zoccai, MD, University La Sapienza, Rome, Italy) and sent electronically to the director of the Investigational Pharmacy at VCU (Robin Sculthorpe, PharmD). Access to randomization log will be restricted and allowed only on an emergency basis, or as requested by the Data Safety and Monitoring Board, or at the end of the study including all data collection. In case of an emergency, a physician treating any patient enrolled in the study may request un-blinding of that individual patient if the physician determines that un-blinding is necessary to make a treatment decision. The PI will contact the VCU Investigational Pharmacy to provide the treatment allocation to the PI, who will then relay the information to the treating physician. If requested by the DSMB, the PI will contact the VCU Investigational Pharmacy to provide the randomization log directly to the DSMB. Upon completion of the study (including completion of all data collection and event adjudication), the PI will request the complete randomization log from the VCU Investigational Pharmacy.

7.3 Patient Compliance with Study Intervention

One goal of the trial is to maximize adherence and retention throughout the study. Adherence will be addressed by count of unused syringes and completion of all study visits. Retention refers to the involvement of study patients throughout the intervention phase of the protocol.

7.4 Concomitant Medications

All concomitant medications will be recorded at each clinic visit. Administration of Anakinra with medications that affect the immune system (i.e. immunosuppressant) or increase the risk of infection (i.e. cancer chemotherapy) is NOT permitted. If a patient requires treatment with such medications, he/she will not be eligible for inclusion in the study. If a patient already enrolled in the study requires such treatments, the investigational treatment (Anakinra or placebo) will need to be discontinued (see reason for discontinuation).

7.5 Standard Medical Management

Patients in the study will receive guideline-based medical treatments as indicated. Such treatments may include β -adrenergic receptor blockers, angiotensin converting enzyme inhibitors or receptor blockers, aldosterone blockers, isosorbide dinitrate, hydralazine, digoxin, aspirin, and statins.

7.6 Cardiopulmonary Test

Upon completion of screening/enrollment, subjects will be scheduled for Visit 1 at the cardiopulmonary exercise suite. A physician-supervised maximal aerobic exercise test will be administered using a metabolic cart that is interfaced with a treadmill. A conservative ramping treadmill protocol will be used. Prior to each test, the oxygen and carbon dioxide sensors will be calibrated using gases of known oxygen, nitrogen, and carbon dioxide concentrations and the flow sensor will also be calibrated using a 3-liter syringe. Subjects will be briefed regarding the protocol and will be requested to exercise to fatigue. 12-lead ECG monitoring will be conducted at baseline, throughout the test and into recovery. Blood pressure will be measured every two minutes using an automated exercise-compatible device (Tango, SunTech Medical). In this technique, expired gases are sampled using a mouthpiece-mounted sensor, and analyzed to continuously measure oxygen (O₂) uptake; the highest 10-second average value for O₂ uptake defines peak oxygen consumption (VO₂ peak in mL•kg⁻¹•min⁻¹). The ventilatory equivalents method will be used to determine VO₂ at ventilatory threshold. Ten second averaged VE and VCO₂ data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO₂ slope via least squares linear regression ($y = mx + b$, m =slope). American Heart Association guidelines for exercise testing contraindications and termination criteria will be followed.

Upon completion of exercise testing, the results of the cardiopulmonary exercise test will be reviewed and discussed with the patients. Patients with angina, abnormal blood pressure or heart rate response, or ECG changes suggestive of coronary ischemia will be excluded from the study.

Subjects will return to the cardiopulmonary exercise suite for the additional visits upon completion of 4 weeks (Visit 2, 28±7 days) or 12 weeks (Visit 3, 84±7 days) of treatment with Anakinra or placebo, or following 12 weeks of wash-out (Visit 4, 168±14 days). At each visit, subjects will undergo a brief physical exam and repeat exercise testing.

7.7 Echocardiogram

Prior to initiation of treatment, the patient will undergo a transthoracic echocardiogram to measure left and right ventricular and atrial dimensions, left and right ventricular systolic function, transmitral flow Doppler spectra, mitral and tricuspidal valve annulus tissue Doppler spectra, ejection time and stroke volume, inferior vena cava, aorta and pulmonary artery diameters and Doppler spectra, according to the recommendations of the American Society of Echocardiography.^[16-18] The echocardiogram will be repeated at each additional visit.

7.8 Blood pressure measurement through ccNexfin finger cuff

A small cuff will be placed on the subject's finger to measure blood flow. A standard blood pressure cuff will then be placed on the arm and inflated for 2-3 minutes. The finger cuff [ccNexfin, Edwards Scientific] will measure changes in blood flow before and after cuff deflation to provide an estimate of flow mediated dilatation—a surrogate marker of endothelial function. The estimated duration of the study is less than 10 min.

7.9 Bioelectrical Impedance analysis (Bio-Impedance)

Bioelectrical Impedance Analysis or Bio-Impedance is a non-invasive, quick and safe technique that allows estimating body composition. Impedance is briefly defined as the property of the electrical ionic conduction of soft tissue where fat and bone are considered poor conductors, however the microampere range developed during the test does not represent any hazard for the patient. The patient will be asked to stay still on the bed, with superior limbs abducted at 30° and the inferior ones at 45°. Four cutaneous electrodes (two on the foot and two on the homolateral hand) are applied. Between two electrodes, at least 5 cm distance is required. A small electricity current is applied to the electrodes. We will measure how the electricity is conducted through the body using a Quantum IV Body Composition Analyzer (RJL Systems) and then, using a dedicated software, we will determine the body composition (water, lean mass and fat). The estimated duration of the study is less than 10 min.

7.10 Stress-Echocardiogram

At visit 1 and visit 3, in correspondence of the CPET, the patient will undergo a limited echocardiogram acquisition prior to initiation of the exercise and after peak exercise. Two dimensional and Doppler images will be acquired to measure LV dimensions in diastolic and systole from the apical 4 chamber view, the pulsed wave and tissue Doppler spectra of the transmitral flow, the mitral annulus, the tricuspidal annulus.

7.11 Questionnaires

Prior to each cardiopulmonary exercise test, subjects will complete the Minnesota Living with Heart Failure and the Duke Activity Status Index (DASI) questionnaires. The Minnesota Living with Heart Failure questionnaire (MLHFQ) is a 21-question graded questionnaire that has been extensively used to measure impairment in quality of life in patients with HF.^[14] The questions are designed to measure a wide range of physical, emotional, social, and mental factors that

contribute to overall quality of life. The DASI is a twelve-item “yes/no” questionnaire that allows for the calculation of perceived functional capacity. Each question describes a different physical activity and asks the subjects if they feel they can perform the task. The questions are weighted according to their degree of physical exertion. The weighted values from the “yes” responses are summed to produce a score in metabolic equivalents.

7.12 Biomarkers assessment

Blood samples will be taken from a peripheral vein at 0, 4, 12 and 24 weeks. Samples will be centrifuged and then refrigerated, and shipped with cold packs within 24 hours to True Health Diagnostic Laboratories LLC., Richmond, VA. The results of the complete blood cell count and basic metabolic profile will be sent to the PI at VCU by email or fax.

Blood samples will be used for analysis of for complete blood cell count, metabolic markers (including lipids and lipoproteins, glycemic control and insulin resistance, liver and renal panel, sterols), inflammatory markers (i.e. high sensitivity CRP) and cardiac biomarkers (i.e. NT-proBNP and troponin I).

One EDTA-containing tube, one SST containing tube, one Serum Separator Clot Activator tube and one PPT tube will be used for analysis of plasma levels of biomarkers by the True Health Diagnostics LLC, Richmond, VA.

7.13 Study Schedule

	Enrollment	Visit 1 (Baseline)	Visit 2 (Week 4)	Visit 3 (Week 12)	Visit 4 (Week 24)	Additional F/U
Screening *	X					
Consent	X					
Clinical assessment **	X	X	X	X	X	X
Investigational therapy		X	X	X		
CPET		X	X	X	X	
Echocardiogram		X	X	X	X	
ccNexFin monitoring		X	X	X	X	
Bio-Impedance		X	X	X	X	
Stress echocardiogram		X		X		
Biomarkers	X	X	X	X	X	

*_Pregnancy test will be performed, if indicated

**_Clinical assessment includes history and physical, medication reconciliation, and assessment of adverse events

7.13 Cost coverage analysis

A cost coverage analysis was conducted prior to the initiation of the trial to determine what constitutes standard of care, which will be billed to the patient or the insurer, and what is considered 'research' which will be paid for with the study budget.

8) ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

Safety parameters will include data deriving from history and physical examination performed at each visit, laboratory data and results of functional and imaging tests. To enhance detection of adverse events between visits, all patients will be encouraged to contact the research team at any time with concerns or any perceived changes in their healthcare status.

Disease-related data (HF-related) will be assessed including changes in symptoms (or new symptoms), functional capacity, vital signs (including weight), renal function, or any significant changes in medications.

Data specific to the treatment will also be assessed. The patient will be asked about symptoms and examined for signs of infection. Considering that Anakinra may mask signs of infection such as fever, a low threshold for further investigation will be advocated. A complete cell count will be measured at each visit to exclude the unusual cases of Anakinra-related neutropenia ($ANC < 1000$), for which suspension of active treatment will be encouraged until return to a value of $ANC > 1,800/mm^3$ (or $> 1,000/mm^3$ if patient is African-American).

Changes to treatment for side-effects or unanticipated problems will be performed without breaking the randomization code, unless deemed necessary for the treatment of the individual patient by the physician, in which case the physician will be made aware while the remainder of the team, especially the investigators performing and interpreting the tests, will be maintained blinded.

The risks of the tests performed have been described above. In order to reduce risk, the procedures will be performed by skilled practitioners in the standard clinical fashion.

Abnormal or incidental findings will be handled on a case by case basis as clinically indicated.

8.2 Data collection

The principal investigator at the site will be provided with a data collection sheets or case report forms on which data about the individual subject will be collected. The subjects will be identified as a consecutive number (i.e. 01, 02, ...08). The data collected on these forms will not contain any personal identifiable information. A database of de-identified data will be created.

8.3 Methods of Timing for Assessing, Recording, and Analyzing Safety Parameters

8.3.1 Adverse Events

All Adverse Effects (AEs) will be recorded on an AE form regardless of causality.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product considered to be causally related to the study treatment or research conduct. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient for medical care, or upon review by an investigator or study coordinator. An event that is considered by the investigator(s) to be expected and related to the natural history of the disease is NOT considered an AE.

All events considered AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate AE form. Information to be

collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis, which would include a physician) and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

Severity of Event: All AEs will be assessed by the study investigator using the following guidelines:

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and may require systemic drug therapy or other treatment.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e. does not include a reaction that might have caused death had it occurred in a more severe form).

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to the intervention: All suspected AEs must have their relationship to study intervention assessed using the terms: associated or not associated. In a clinical trial, the study intervention must always be a suspect. To help assess, the following guidelines are used to assess causality:

- Definitely related: The event is temporally related to the administration of the study intervention and, in the opinion of the investigator, no other etiology explains the event.
- Probably related: The event is temporally related to the administration of the study intervention and represents, in the opinion of the investigator, the most plausible explanation of the event.
- Possibly related: The event is temporally related to the administration of the study intervention but, in the opinion of the investigator, it does not represent the most likely explanation of the event.
- Definitely Unrelated: The event is temporally independent of study intervention and/or the event appears, in the opinion of the investigator, to be explained by another etiology.

8.3.2 Serious Adverse Events

An SAE is any adverse event/experience occurring between baseline assessments and the patients final study visit that results in any of the following outcomes and is considered by the investigator(s) to be unexpected or not consistent with the natural history of the disease:

- Death
- Life threatening (subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All the unexpected SAE will be promptly (within 24 hours) reported to the local IRB and DSMB (see reporting procedures). The DSMB report to the investigators will be forwarded to the NHLBI Program Officer, including the discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 14 days for unanticipated problem that is not an SAE or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings).

8.4 Reporting Procedures

8.4.1 Serious Adverse Events

All unexpected AEs that result in death or are otherwise reportable SAEs or AEs will be reported promptly to the Data Safety Monitoring Board (DSMB) and the IRB within 1 business day of knowledge of the event.

AEs (serious or nonserious) that transpire secondary to an overdose must also be reported to the DSMB within 1 business day of knowledge of the event, using an AE form.

The SAE form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and, if a reportable adverse event as defined herein, forwarded to the DSMB within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the DSMB of the event and completing the SAE form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report.

8.5 AE/SAE Data Collection

When an AE/SAE is suspected, it is the responsibility of the investigator(s) to review all documentation (e.g. hospital progress notes, laboratory and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding a suspected AE/SAE on the AE form. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.6 The Data and Safety Monitoring Board (DSMB)

For this study, the DSMB is composed of a coordinator and 5 voting members, including a cardiologist from University of Florida in Jacksonville, Florida, a heart failure specialist, a general cardiologist, an infectious disease specialist, and a general internal medicine specialist. The composition of the DSMB has been approved by the VCU IRB. The DSMB will meet every 6 months or sooner in case of unanticipated serious adverse events. The DSMB coordinator will provide the board members with data regarding screening, enrollment, adverse events and withdrawals, and he/she will not participate in the voting. The board members may request unblinding at any time. Upon request of the DSMB (following positive vote by 3 or more members), the coordinator will retrieve the randomization code for one or more individual patients (as needed). If necessary the DSMB will inform the investigators of the unblinding of the randomization code, if not necessary the investigators (and the patients) will be kept blinded. The DSMB may request an expert opinion by one or more non-members, however only the DSMB members will vote on any individual issue. The DSMB (following positive vote by 3 or more members) may request temporary or permanent halting of the study (see halting rules), or interruption of treatment of one or more patients. The minutes from each meeting will be distributed to the board members, NHLBI Program Officer, and to the IRB, and not to the investigators unless specifically requested by the DSMB. A brief conclusive statement addressing whether the study should continue as planned or not will be provided to the investigators and the IRB every 6 months. The investigators will provide the NHLBI staff with reports from the DSMB and the IRB in a timely fashion (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings). See Appendix – DSMB Chapter.

8.7 Regulatory Reporting

This study is conducted in accordance to the NIH Good Clinical Practice guidelines. An Investigational New Drug use waiver from the Division of Cardiovascular & Renal Products, Center for Drug Evaluation & Research, Food & Drug Administration was given to Dr. Abbate. The study protocol, consent, and Data and Safety Monitoring Plan has been approved by the VCU IRB. The investigators will provide the NHLBI staff with reports from the DSMB and the IRB in a timely fashion (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 15 calendar days for all non-fatal, non-life threatening

unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems).

8.8 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, whichever occurs first. All AEs and SAEs documented at a previous visit/contact and designated as ongoing, will be reviewed at subsequent visits/contacts, where the designation may remain ongoing. The investigator will ensure that the follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. SAEs that are ongoing at the time of the subjects final study visit/contact will be documented as ongoing.

8.9 Halting Rules

The DSMB will monitor the progress of the present trial. No interim efficacy analyses are planned; however an interim analysis could be performed at any time to assess efficacy and futility, if requested by the 3 or more members of the DSMB. The DSMB will meet regularly to review safety data every 6 months (or sooner in case of unanticipated serious adverse events). All meetings and actions taken by the committee will be recorded along with the reasons for the actions. These documents will include any data summaries or analyses provided to the DSMB and will remain confidential until the study is concluded. The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. If no safety concerns are found, enrollment will continue until the target sample size is reached.

9) ADJUDICATION OF CLINICAL EVENTS

9.1 Event-adjudicating committee

The event-adjudicating committee is composed of a general cardiologist, a cardiologist with training in heart failure, and a general internal medicine specialist. The committee will meet at the end of the study and adjudicate all the events. The committee will be blinded to treatment allocation. In order to favor allocation concealment, the committee will also be blinded to C-reactive protein levels, which may be affected by treatment.

9.2 Definition of the events

The events adjudicated will include:

- Death;
- Cardiac death (in which a direct cause attributable to cardiac disease is present);
- Sudden cardiac death (in which cardiac death occurred out of the hospital and suddenly; or in the hospital due to ventricular arrhythmias unrelated to other concomitant cardiac conditions);

- Non-cardiac death (in which the event of death is considered not to be a direct consequence of cardiac disease);
- Hospitalization for any cause;
- Hospitalization for heart failure (in which the primary diagnosis for hospitalization is decompensated heart failure established as the finding at admission of all 2 conditions listed: a. dyspnea or respiratory distress or tachypnea at rest or with minimal exertion; b. evidence of elevated cardiac filling pressure or pulmonary congestion (at least one of the conditions must be met: pulmonary congestion/edema at physical exam OR chest X-ray; plasma BNP levels ≥ 200 pg/ml; or invasive measurement of left ventricular end-diastolic pressure >18 mmHg or of pulmonary artery occluding pressure (wedge) >16 mmHg)
- Acute myocardial infarction, as defined by the WHO consensus statement;
- Unstable angina, or need for coronary revascularization;
- Cardiac tachy-or brady-arrhythmias leading to a new hospitalization or to prolongation of hospital stay;
- Acute renal failure (defined as an increase in plasma creatinine levels of 50% or 0.5 mg/L);
- Acute respiratory failure (not due to heart failure);
- Sepsis or other serious infection requiring antibiotic therapy;
- Acute stroke.

The analysis will consider time to first event and time to each event. It will also consider event rates at 1, 3 and 6 months, in order to favor comparisons with other studies. The number of days free of hospitalization during the first 1, 3 and 6 months will also be measured and compared between groups.

9.3 Implications of the findings of the event-adjudicating committee

The events will be adjudicated only after the completion of the study, and therefore the findings by the committee will have no implications on the conduct of the study.

10) DISCONTINUATION OF TREATMENT AND WITHDRAWAL

10.1 Reasons for Discontinuation of Treatment or Withdrawal from the Study

Patients may withdraw from the study at any time. The investigators can withdraw any patient at any time from the study if medically necessary. It will be extremely important to obtain complete follow-up data on each patient, except on those who withdraw consent to release such information. It will be documented whether or not each patient completed the study. If for any reason the study treatment or observations were discontinued, the reasons will be recorded and the IRB will be informed.

Reasons for discontinuation of Anakinra (or placebo):

- 1) Neutropenia (ANC <1000)*;
- 2) Systemic infection (sepsis)*;
- 3) Surgery *;
- 4) Cancer;

- 5) Hypersensitivity reaction (rash, anaphylaxis);
- 6) Severe injection site reactions *;
- 7) Need for immunosuppressant therapy;
- 8) Acute myocardial infarction or stroke.

* treatment may be restarted after condition resolved

10.2 Handling of Withdrawals

Loss to follow-up can occur due to patients' withdrawal or unreported death. Patients that have withdrawn from treatment will still be offered to complete all the functional assessments to analyze data in an intention-to-treat strategy. If patients are lost to follow up and their clinical condition cannot be established (alive vs dead, hospitalized vs not), they will be excluded from the initial analysis, and then reintroduced for sensitivity analysis considering all potential outcomes.

10.3 Termination of Study

The decision regarding continuation or termination of the study will be solely based on safety data, and will be made by the DSMB. Interim analyses will be performed by the DSMB upon request by the co-PIs. The co-PIs will meet every month (or sooner in case of unanticipated serious adverse events) to discuss enrollment, withdrawals, and adverse events. If protocol modifications are warranted, close consultation with the DSMB and IRB will be required, and their approval will be needed.

11) RECRUITMENT STRATEGIES

The investigators or coordinators in the study will screen and evaluate patients evaluated at the Virginia Commonwealth University Health System for heart failure. Such patients are likely to be found in the Department of Internal Medicine and the Department of Emergency Medicine. No advertisement strategies are planned at this time.

12) STATISTICAL CONSIDERATIONS

12.1 Study Hypothesis

We hypothesize that IL-1 blockade with Anakinra will improve aerobic exercise performance and reduce hospital admission rates in patients with HF and preserved ejection fraction (HFpEF). As the first step in testing this hypothesis, we propose a randomized, double-blinded, pilot study to determine the effect of anakinra on aerobic exercise performance over the course of 6 months. Although this pilot study will not be powered to detect differences in the 3-month and 6-month hospital admission rates, we believe this study will provide an estimate of the potential effect. An improvement in aerobic exercise performance alone would represent a valuable achievement in

this HF population, and would provide the rationale—especially if paired with a signal showing reduced readmission rates—for a subsequent Phase III clinical study to evaluate IL-1 blockade on the key outcomes of HF morbidity and mortality.

12.2 Sample Size Considerations

The sample size for this pilot study is calculated according to the primary endpoint of difference in interval change in peak VO_2 at 12 weeks between anakinra and placebo. Given an expected average peak VO_2 of 15 ± 3.5 mL/kg/min for HF patients, 40 subjects randomized to anakinra and 20 subjects randomized to placebo (2:1 randomization) would provide approximately 95% power to detect a difference of $3.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (23% improvement) in peak VO_2 . An improvement of $3.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ equals 1 metabolic equivalent and is typically associated with a 13–15% reduction in mortality. A conservative estimate of 20% loss to follow-up or withdrawal would retain >90% power.

12.3 Statistical Analysis

12.3.1 Demographics and Baseline Characteristics

Baseline measurement and demographic characteristics will be summarized for the patients into each of the treatment arms. Descriptive summaries of continuous measurements will consist of means, standard deviations and 95% confidence intervals; if the measurements have markedly non-normal distributions, then medians and interquartile ranges will be provided instead. Descriptive summaries of categorical measurements will consist of frequencies, proportions and 95% confidence intervals on those proportions. The summaries for each measurement will be provided separately for each treatment group.

12.3.2 Analysis of the Primary Endpoint

The data will be collected and electronically transferred to the core laboratory at the University of Illinois, Chicago, IL, where Dr. Ross Arena, PhD, will analyze data at the end of the study. After locking the database, he will be provided a group allocation according to treatment A or B (blinded to real treatment). Dr. Arena and Dr. Lu (biostatistician) will analyze the data according to blinded group allocation and the description of the group allocation will be disclosed only after completion of the analysis. The differences in interval changes between the treatments will be compared using random-effect analysis of variance for repeated measures to analyze the effects of time and group allocation. Unadjusted p values will be reported throughout, with statistical significance set at the 2-tailed 0.05 level. All analyses will be based on a 'complete case' approach.

12.3.3 Analysis of Secondary Endpoints

The data will be collected and electronically stored. The analysis will be performed at the conclusion of the study as described above. For statistical analysis, all values will be reported as the median and interquartile range for potential deviation from Gaussian distribution. The differences between treatment groups will be computed using the Wilcoxon signed-rank test for continuous variables or Fisher's exact test for discrete variables.

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DSMB CHARTER

Charter, Data and Safety Monitoring Board for

NHLBI 1R34HL118348-01A1

Interleukin-1 blockade in heart failure with preserved ejection fraction:

Diastolic Heart Failure Anakinra Response Trial -2

(D-HART2)

Updated on August 13, 2014

Executive Secretary: Christine DeWilde, RN – dewillect@vcu.edu

1 Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the study: **Interleukin-1 blockade in heart failure with preserved ejection fraction: Diastolic Heart Failure Anakinra Response Trial -2 (D-HART2)**

hereafter referred to as “D-HART2”.

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2 Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of **D-HART2**.

The DSMB is an independent group advisory to the investigators, and is required to provide recommendations about starting, continuing, and stopping the study **D-HART2**. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Participant safety
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Notification of and referral for abnormal findings
- Efficacy of the intervention at study termination (no interim analyses planned)

3 Organization and Interactions

Communication with DSMB members will be primarily through the DSMB executive secretary, Christine DeWilde, RN, Officer and the investigators at Virginia Commonwealth University (VCU). It is expected that study D-HART2 investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

a. DSMB Members and NHLBI Program Staff

DSMB members and their expertise are listed in Appendix A. Consistent with NHLBI policy, the DSMB is assigned an Executive Secretary (ES) to provide an unbiased staff interface for the DSMB, especially during executive sessions. The ES is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes.

b. Scheduling, Timing, and Organization of Meetings

DSMB meetings will be held at the Virginia Commonwealth University, Richmond, VA, unless otherwise specified. For DSMB members residing outside of Virginia, telephone participation will be allowed for all meetings. The purpose of the first meeting is to review and discuss this Charter, to provide an overview of study D-HART2 activities, to review and make recommendations about the protocol(s), and to determine the frequency of interim analyses and whether data will or will not be masked to identity of randomized groups. Enrollment in a study cannot begin until the DSMB's recommendation for approval of the protocol has been made and IRB approval for the protocol including the DSMP has been obtained.

Meetings are usually held approximately twice a year, every 6 months, with additional meetings or conference calls scheduled as needed. Once the DSMB has established its working routine, consideration can be given to replacing one or both meeting per year with a conference call, if the agenda permits. Meetings and conference calls will be scheduled and the agenda will be developed by the ES in close consultation with the Chair and the NHLBI Program Officer.

- For this DSMB, meetings will be held twice per year.
- The DSMB will monitor the progress of the present trial.
- No interim efficacy analyses are planned; however an interim analysis could be performed at any time to assess efficacy and futility, if requested by the 3 or more members of the DSMB.
- The DSMB may choose to stop enrollment on the basis of safety data observed. If safety concerns are found, further enrollment will not be allowed until issues are resolved. If no safety concerns are found, enrollment will continue until the target sample size is reached.

The agenda for DSMB meetings and calls will be drafted by the ES in consultation with the Chair, investigators and the NHLBI Program Officer. The ES will finalize the agenda after

consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the ES 4 weeks before each meeting or call to the DSMB members, investigators, and the NHLBI Program Officer.

The ES will collect and document all potential conflicts of interest from each member of the DSMB related to the design, conduct, interpretation, and publication of the study. Before each meeting, when the agenda is sent out, the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since last meeting. This review will be conducted in addition to the review for conflicts of interest conducted by the VCU IRB at the time of initial IRB approval. If a new conflict is reported, the Chair and staff will determine if the conflict limits the ability of the DSMB member to participate in the discussion. The DSMB also will review adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct.

It is expected that all DSMB members will attend every meeting and call. However, it is recognized that this may not always be possible. Quorum for voting is considered to be half the number of standing members plus one. The Board may wish to decide if particular expertise is needed within the quorum for the meeting to be valid. All standing Monitoring Board members are voting members. The Board may also wish to decide in advance whether *ad hoc* members can vote.

A quorum of this DSMB is considered to be 3 members out of total 5.

c. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, information will be presented to the DSMB by the Study Investigators and the NHLBI Program Staff as appropriate, with time for discussion.
- During the **closed sessions**, the DSMB will discuss confidential data from the study D-HART2, including information on efficacy and safety by treatment arm, if available. The DSMB will decide whether to remain masked to the treatment assignments at each meeting. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session. NHLBI Program Officer would join the session only at the discretion of the Chair.

The DSMB may elect to hold an **executive session** in which only the DSMB members, NHLBI Program Officer (at the discretion of the Chair) and the ES are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert)

If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators and NHLBI Program Officer to ask questions to clarify the recommendations, if necessary. The meeting is then adjourned.

d. Reports of DSMB Deliberations

- Formal minutes: The ES is responsible for the accuracy and transmission of the formal DSMB minutes, within 14 days of each meeting or call. These minutes prepared to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. Prior to submission to the investigators and the NHLBI Program Officer, minutes will be reviewed by the DSMB Chair for final review and approval. The DSMB Chair may sign the minutes or indicate approval electronically via email. Then, the minutes are sent to the investigators and the NHLBI Program Officer.
- Reports to IRBs: The investigators will prepare a memo documenting DSMB's deliberations and recommendations and send the memo to VCU IRB and NHLBI Program Officer.
- The DSMB report to the investigators will be forwarded to the NHLBI Program Officer, including the discussion of the concerns, and the basis for any recommendations that the DSMB has made in response to the concerns (within 7 calendar days if fatal or life-threatening unexpected, suspected serious adverse reactions; or within 14 days for unanticipated problem that is not an SAE or within 15 calendar days for all non-fatal, non-life threatening unexpected, suspected serious adverse reactions, or within 30 days of receipt of the DSMB or IRB report for all other unanticipated problems or scheduled meetings).

e. Reports to the DSMB

For each meeting, the investigators will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB should discuss at the first or subsequent meetings what data they wish to review and how it should be presented. The regular reports to the DSMB will contain blinded data for all enrolled subjects. If necessary, the DSMB may request un-blinding of the data, in which case, the DSMB will request that the randomization log be sent to the study biostatistician (Juan Lu, PhD), who will then prepare an un-blinded report for the DSMB.

f. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The final plan, whether part of a research protocol or separate document, will be maintained as an appendix to this charter. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial (if applicable). These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons (if applicable).

Appendix A: DSMB members**Dominick Angiolillo, MD, PhD DSMB Chair**

Dr. Angiolillo is an Associate Professor of Medicine in Cardiology at the University of Florida in Jacksonville. He is board certified in Cardiology and Interventional Cardiology, and serves as Medical Director for the Cardiovascular Research Program in the division of Cardiology.

<http://www.hscj.ufl.edu/directory/bio.aspx?id=1318>

Richard Cooke, MD DSMB Member

Dr. Cooke is an Associate Professor of Medicine in Cardiology at the Virginia Commonwealth University, and is the Chief of the Advanced Heart Failure Service in the VCU Pauley Heart Center. Dr. Cooke is board-certified in Internal Medicine, Cardiology, Heart Failure, and Interventional Cardiology. <http://www.pauleyheart.vcu.edu/staff/cooke.html>

Gonzalo Bearman, MD DSMB Member

Dr. Bearman is a Professor of Medicine and serves as Chief of the Division of Infectious Disease as well as Hospital Epidemiologist. Dr. Bearman is Board Certified in Internal Medicine, Infectious Diseases, and General Preventive Medicine and Public Health.

Ion Jovin, MD, PhD DSMB member

Dr. Jovin is an Associate Professor of Medicine in Cardiology, and serves as Director of the Cardiac Catheterization Laboratories at the Hunter McGuire Veterans Administration Medical Center in Richmond, VA. Dr. Jovin is board certified in Cardiology and Interventional Cardiology.

<http://www.pauleyheart.vcu.edu/staff/jovin.html>

Jeffrey Kushinka, MD DSMB member

Dr. Kushinka is an Associate Professor in the Division of General Internal Medicine, has served as Interim Chair for 2 years. He is also the clerkship director for 3rd Medical Students and an Associate Program Director for the Internal Medicine Residency Program. Dr. Kushinka is board certified in Internal Medicine.

Appendix B: Case Report Forms

- Screening and Enrollment form (1 page)
- Individual Patient Cover Sheets (2 pages)
- Individual Visit Assessment Form (5 pages)
- Adverse Event reporting form (1 page)

D-HART2**Screening and enrollment form**

Subject number: D-HART2 _____ Initials _____ Date _____

INCLUSION CRITERIA: {All 6 criteria need to be met}

D Symptoms and signs of heart failure (NYHA II-III)**D Recent Imaging Study (<12 months) showing LVEF>50% and LVEDVI<97ml/m²****D Evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness as shown by one of the following:**

- o Invasive Hemodynamic measurements (mPCW >12 or LVEDP>16mmHg)
- o Tissue Doppler Echocardiogram, $E/A > 15$
- o Tissue Doppler Echocardiogram, $E/A < 8-15$ and one additional criterion ($E/A < 0.5$ and $DT > 280$ ms, LVH, left atrial enlargement, prior atrial fibrillation)
- o BNP>200pg/ml (not due to a concomitant disease such as pulmonary arterial hypertension, pulmonary embolism, acute renal failure, or other)

D The patient is 2-21 years old, and willing and able to provide informed consent.**D The patient is willing and able to comply with the protocol (i.e. self administration of the treatment, and exercise protocol)**

EXCLUSION CRITERIA (check only if applicable -7 patient excluded):

- o Concomitant conditions or treatments which would affect completion of the study or interpretation of the study tests including but not limited to the following conditions: physical inability to walk or run on a treadmill, angina or evidence of spontaneous or inducible ischemia, uncontrolled arterial hypertension, atrial fibrillation (or other arrhythmias), moderate to severe valvular heart disease, chronic pulmonary disease, anemia (Hgb<10 g/dl)
- o Persistent or chronic atrial fibrillation (prior history is not an exclusion if patient is in sinus rhythm)
- o Active infection including chronic infection
- o Active cancer (or prior diagnosis of cancer within the past 10 years)
- o Anticipated need for surgery
- o Recent (<14 days) or active use of immunosuppressive drugs (including but not limited to high-dose corticosteroids [>1 mg/kg of prednisone equivalent], TNF- α blockers, cyclosporine) not including NSAIDs or corticosteroids used for IV dye allergy only)
- o Chronic auto-immune or auto-inflammatory disease (including but not limited to rheumatoid arthritis, systemic lupus erythematosus)
- o Active cancer (or prior diagnosis of cancer within the past 10 years)
- o Neutropenia (absolute neutrophil count<1,800/mm³ [or <1,000/mm³ in African-American patients])
- o Severe impairment in renal function (estimated glomerular filtration rate <30 ml/kg*min)
- o Recent or planned use of vaccination with live attenuated viruses
- o Allergy to rubber or latex
- o Allergy to products derived from Escherichia coli
- o Pregnancy or breastfeeding

Eligibility criteria verified and consenting completed by _____ on _____ (date)

D Patient given a copy of the informed consent and sufficient time to read and have questions, answered.**D The original signed copy is stored for research, a signed copy is given to the patient, and an additional copy is placed in the chart.****D Laboratory test for screening CRP sent**

Screening plasma C-reactive protein levels >2 mg/L -7 verified on ____/____/____ by _____

HM2000018 – Interleukin-1 Blockade in heart failure with preserved ejection fraction (O-HART2)

Participant Study ID:			
<ul style="list-style-type: none"> - Was the patient re-admitted between baseline and 4-week FU? NO / YES - Was the patient re-admitted between 4-week FU and 12-week FU? NO / YES - Was the patient re-admitted between 12-week FU and 24-week FU? NO / YES 		<p>1st Batch of Drug Dispensed to Participant Date: __/__/____ #of syringes dispensed: ____ Date for 4-week follow-up: __/__/____</p> <p>Drug Returned by Participant at 4-week FU Date: __/__/____ #of syringes returned: ____</p> <p>2nd Batch of Drug Dispensed to Participant Date: __/__/____ #of syringes dispensed: ____ Date for 12-week follow-up: __/__/____</p> <p>Drug Returned by Participant at 12-week FU Date: __/__/____ #of syringes returned: ____</p>	
Eligibility Confirmed on __/__/____ Signed/Performed by: _____		If Re-Consented: Date ICF signed: __/__/____ Withdrew Consent: Date: __/__/____ Reason? _____	
Informed Consent: Version __/__/____ IRB approval __/__/____; signed on __/__/____		Notes:	
Randomization: __/__/____		Notes:	
Study Time Point	Study Procedure	Completed	Notes
Screening / /	Blood Draw (screening – VCU)		
	Echocardiogram (prior enrollment)		
Baseline __/__/____	Note in CIS re: Clinical Trial/ICF Process		
	Blood Draw (baseline-HDL)		
	Echocardiogram		
	FMD		
	BIA		
	Dietary Assessment		
	Concomitant Rx		
	Baseline History		
	CPET		
	Echo-stress		
	Invest. Drug Dispensed (1 st Batch)		
	Drug Dose #1 administered		
	Blood Draw (4-week HDL)		
	Echocardiogram		
	FMD		

HM2000018 - Interleukin-1 Blockade in heart failure with preserved ejection fraction ID: HART21			
4-week FU _ _ _	BIA		
	CPET		
	Concomitant Rx		
	AE review/History		
	Invest. Drug Dispensed (2nd Batch)		
	Other:		
12-week FU _ _ _	Blood Draw (12-week HDL)		
	Echocardiogram		
	FMD		
	BIA		
	Dietary Assessment		
	CPET		
	Echo-stress		
	Concomitant Rx		
	AE review/History		
	Other:		
24-week FU _ _ _	Blood Draw (12-week HDL)		
	Echocardiogram		
	FMD		
	BIA		
	Dietary Assessment		
	CPET		
	Concomitant Rx		
	AE review/History		
Other:			
Additional Notes: • SAEs Reported? • Deviations?			

D-HART2 Subject # _____ Initials _____ Date on Enrollment _____

Baseline

☐ Inclusion/exclusion criteria reviewed; ☐ consent obtained

☐ Heart Failure symptoms – NYHA II ☐ or III ☐

Current symptoms and signs: (check all that apply)

☐ shortness of breath; ☐ orthopnea; ☐ paroxysmal nocturnal dyspnea

☐ chest pain; ☐ tiredness/fatigue; ☐ edema (symptom); ☐ abdominal fullness

On exam: ☐ pitting edema, ☐ S3 gallop, ☐ S4 gallop, ☐ JVD, ☐ rales

Notes _____

Medical History: (check all that apply)

☐ Ischemic heart disease; ☐ Prior PCI; ☐ Prior CABG; ☐ Prior CVA; ☐ Hypertension

☐ Diabetes; ☐ Hyperlipidemia; ☐ Current Tobacco user; ☐ Peripheral Vase Disease

☐ Chronic Kidney Disease; ☐ Chronic Obstructive Lung Disease; ☐ DVT/PE;

☐ Obstructive sleep apnea; ☐ Morbid obesity, check ☐ if BMI >35 and ☐ if >40

Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²

Blood Pressure: _____ mmHg HR: _____ min

Notes _____

Planning: (check all completed)

☐ Baseline echocardiogram Doppler

☐ Nexfin and Bioelectrical impedance analysis

☐ Dietary assessment

☐ Baseline cardiopulmonary exercise test

☐ Heart failure questionnaires

☐ Baseline stress echocardiogram Doppler

☐ Labs sent to HDL

☐ Recording of current medications

☐ Dispensing of investigational drug (for 35 days) by _____

☐ Patient education on drug handling, storage, and self-administration

☐ Outpatient Hospital Follow up on day 28 (24-32) on _____ at _____

Notes _____

D-HART2 Subject# _____ Initials _____ Date on Enrollment _____

Follow up visit: 4 weeks

Date of enrollment. ____-____-____ Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ 1 heart failure symptoms, NYHA class (1-?IV), check ☐ 1 if re-hospitalization
☐ 1 re-hospitalization for other cause (complete dedicated sheet)
☐ 1 death, check ☐ 1 if presumed cardiac death, check ☐ 1 if sudden death
☐ 1 interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)

- ☐ 1 shortness of breath; ☐ 1 orthopnea; ☐ 1 paroxysmal nocturnal dyspnea
☐ 1 chest pain; ☐ 1 tiredness/fatigue; ☐ 1 edema (symptom); ☐ 1 abdominal fullness
 On exam: ☐ 1 pitting edema, ☐ 1 S3 gallop, ☐ 1 S4 gallop, ☐ 1 JVD, ☐ 1 rales

Notes _____

Past Medical History: (changes vs prior —new diagnoses)

- ☐ 1 _____; ☐ 1 _____; ☐ 1 _____ · ☐ 1 _____

Notes _____

Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²

Blood Pressure: _____ mmHg HR: _____ min

Planning: (check all completed)

- ☐ 1 F/u echocardiogram Doppler
☐ 1 Nexfin and Bioelectrical impedance analysis
☐ 1 F/u cardiopulmonary exercise test
☐ 1 F/u stress echocardiogram Doppler (only at the 3 months visit)
☐ 1 Labs sent to HDL
☐ 1 Updating current medications
☐ 1 Assessment of compliance with investigational drug performed by _____
 (used syringes _____ · returned syringes _____)
☐ 1 Assurance of compliance
☐ 1 Dispensing of investigational drug (for 49 days) by _____
☐ 1 Scheduling next appointment on _____ at _____

D-HART2 Subject # _____ Initials _____ Date on Enrollment _____

Follow up visit: 12 weeks

Date of enrollment _____ Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ 1 heart failure symptoms, NYHA class (I-IV), check ☐ 1 if re-hospitalization
☐ 1 re-hospitalization for other cause (complete dedicated sheet)
☐ 1 death, check ☐ 1 if presumed cardiac death, check ☐ 1 if sudden death
☐ 1 interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)

- ☐ 1 shortness of breath; ☐ 1 orthopnea; ☐ 1 paroxysmal nocturnal dyspnea
☐ 1 chest pain; ☐ 1 tiredness/fatigue; ☐ 1 edema (symptom); ☐ 1 abdominal fullness
 On exam: ☐ 1 pitting edema, ☐ 1 S3 gallop, ☐ 1 S4 gallop, ☐ 1 JVD, ☐ 1 rales

Notes _____

Past Medical History: (changes vs prior – new diagnoses)

- ☐ 1 _____; ☐ 1 _____; ☐ 1 _____ · ☐ 1 _____

Notes _____

Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²
 Blood Pressure: _____ mmHg HR: _____ min

Planning: (check all completed)

- ☐ 1 F/u echocardiogram Doppler
☐ 1 Nexfin and Bioelectrical impedance analysis
☐ 1 Dietary assessment
☐ 1 F/u cardiopulmonary exercise test
☐ 1 F/u stress echocardiogram Doppler (only at the 3 months visit)
☐ 1 Labs sent to HDL
☐ 1 Updating current medications
☐ 1 Assessment of compliance with investigational drug performed by _____
 (used syringes _____ · returned syringes _____)
☐ 1 Assurance of compliance
☐ 1 Scheduling next appointment on _____ at _____

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D-HART2 Subject# _____ Initials _____ Date on Enrollment _____

Follow up visit: 24 weeks

Date of enrollment _____ Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ heart failure symptoms, NYHA class (I-IV), check ☐ if re-hospitalization
☐ re-hospitalization for other cause (complete dedicated sheet)
☐ death, check ☐ if presumed cardiac death, check ☐ if sudden death
☐ interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)

- ☐ shortness of breath; ☐ orthopnea; ☐ paroxysmal nocturnal dyspnea
☐ chest pain; ☐ tiredness/fatigue; ☐ edema (symptom); ☐ abdominal fullness
 On exam: ☐ pitting edema, ☐ S3 gallop, ☐ S4 gallop, ☐ JVD, ☐ rales

Notes _____

Past Medical History: (changes vs prior – new diagnoses)

- ☐ _____; ☐ _____; ☐ _____

Notes _____

Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²

Blood Pressure: _____ mmHg HR: _____ min

Planning: (check all completed)

- ☐ F/u echocardiogram Doppler
☐ Nexfin and Bioelectrical impedance analysis
☐ F/u cardiopulmonary exercise test

☐ F/u stress echocardiogram Doppler (only at the 3 months visit)☐ Labs sent to HDL☐ Updating current medications

☐ Assessment of compliance with investigational drug performed by _____
 (used syringes _____ returned syringes _____)

☐ Assurance of compliance☐ Scheduling next appointment on _____ at _____

D-HART2 Subject# _____ Initials _____ Date on Enrollment _____

Unscheduled visit

Date of enrollment _____, Date of F/U visit _____

Clinical conditions: (check all that apply)

- ☐ heart failure symptoms, NYHA class (1-4), check ☐ if re-hospitalization
☐ re-hospitalization for other cause (complete dedicated sheet)
☐ death, check ☐ if presumed cardiac death, check ☐ if sudden death
☐ interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)

- ☐ shortness of breath; ☐ orthopnea; ☐ paroxysmal nocturnal dyspnea
☐ chest pain; ☐ tiredness/fatigue; ☐ edema (symptom); ☐ abdominal fullness
 On exam: ☐ pitting edema, ☐ 3+ gallop, ☐ 4+ gallop, ☐ JVD, ☐ rales

Notes _____

Past Medical History: (changes vs prior – new diagnoses)

☐ _____; ☐ _____; ☐ _____ · ☐ _____

Notes _____

Body weight: _____ kg/_____ lb Height: _____ m/_____ ft BMI: _____ kg/m²
 Blood Pressure: _____ mmHg HR: _____ min

Planning: (check all completed)

- ☐ Scheduling next appointment

Notes _____

D-HART2 study

Version April 7, 2015

D-HART2 Study EVENT FORM**D-HART2 Subject _____ Initials _____**

Hospitalization, date _____

Death, date _____

D Acute Decompensated Heart Failure as
primary diagnosis (see Protocol)D Acute Coronary Syndrome as primary
diagnosis

D Arrhythmia as primary diagnosis

D Acute Renal Failure

D Acute Respiratory Failure (not due to
heart failure)

D Sepsis, or Severe Infection

D TIA/Stroke

D Other (Specify _____)

Other events, date _____

(not leading to hospitalization)

D Injection site reaction

D Rash D Fever

D Infection (requiring antibiotic tx D)

D Nausea/Vomiting/Diarrhea

D Others: (Specify _____)

Interruption of Treatment,
date _____

D Mandated by protocol

D Decision made by patient

D Out of hospital and sudden

D In-hospital, associated with ventricular
arrhythmia not secondary to other
cardiac diseaseD In-hospital, associated with acute
cardiac issueD In-hospital, associated with acute non
cardiac issue (Specify _____)

D Other (Specify _____)

D Unknown

ADVERSE EVENT: YES D NO D**ANTICIPATED D, NOT ANTICIPATED D****SEVERITY:****MILD O; MODERATE O; SERIOUS O****RELATED TO RESEARCH:****UNRELATED O; POSSIBLY O;****PROBABLY O; DEFINITELY O****IF SERIOUS, UNANTICIPATED, and RELATED TO RESEARCH -7
REPORT IMMEDIATELY TO THE PRINCIPAL INVESTIGATOR(s)**_____
Completed By, Name_____
Signature_____
Date

Attach de-identified Notes from chart or notes (check D if not available)

Principal Investigator(s)_____
Signature_____
Date

Prompt report to the IRB/DSMB needed D completed D by _____ on _____